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Article

Pattern Electroretinography and Visual Evoked Potentials Provide Clinical Evidence of CNS Modulation of High- and Low-Contrast VEP Latency in Glaucoma

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Purpose: Both pattern electroretinography (PERG) and visual evoked potentials (VEP) can be performed using low- (15%; Lc) and high- (85%; Hc) contrast gratings that may preferentially stimulate the magno- and parvocellular pathways. We observed that among glaucomatous patients showing only one VEP latency deficit per eye, there appeared to be a very strong tendency for an Hc delay in one eye and an Lc delay in the other.

Methods: Diopsys NOVA-LX system was used to measure VEP Hc and Lc latency among a clinical glaucoma population to find all individuals with either a single Hc or Lc latency abnormality in each eye (group 1), or with greater than 0 and less than 4 Hc or Lc VEP latency abnormalities in the two eyes (group 2) to determine whether a significant inverse correlation existed for these values in either group. Hc and Lc PERG data were also evaluated to assess associated retinal ganglion cell responses.

Results: A strong inverse correlation ($P = 0.0000003$) was observed between the Hc and Lc VEP latency values among the 64 eyes in group 1. Group 2 provided a comparable result ($n = 143$; 286 eyes; $P = 0.0005$). PERG ($n = 81$; 162 eyes) also showed strong bilateral symmetry for magnitude values ($P < 0.0001$ for both Lc and Hc in groups 1 and 2).

Conclusions: Bilateral retention of both low-resolution/high-speed and high-resolution/low-speed function may persist with both eyes open despite symmetrically pathologic retinal ganglion cell PERG waveform asynchrony for Hc and Lc stimuli in the paired eyes.

Translational Relevance: Clinical electrophysiology strongly suggests binocular compensation for dynamic dysfunction operates under central nervous system (CNS) control in glaucoma.

Introduction

Glaucoma is among the World's leading causes of permanent vision loss.[1] While objective screening and progressive treatment paradigms have helped diminish many other major worldwide causes of vision loss, the proportion of global blindness attributable to glaucoma continues to increase (by 50% between 1990 and 2012).[2] Current projections indicate that by 2040 glaucoma will afflict 112 million people.[3]

Open angle glaucoma is an age-related neurodegeneration, similar at the cell biologic level to Alzheimer and Parkinson Disease.[4,5] Confirmation of therapeutic efficacy requires clinical evidence that the pathologic processes leading to functional and structural damage have been mitigated. Glaucomatous visual compromise is characterized functionally

using perimetry to detect and monitor progression of visual field (VF) abnormalities that reflect an uncertain combination of permanent ganglion cell axonal loss and potentially reversible preapoptotic axonal dysfunction. The actual functional wellbeing of surviving axons thus cannot be deduced from any single VF examination, because severe defects may remain stable, and mild defects may progress. Retinal nerve fiber layer (RNFL) analysis typically provides spatial correspondence of sectorial axonal thinning with areas of permanent VF loss[6,7] but cannot readily provide any indication of the functional integrity of the remaining extant axonal population. A combination of repeated perimetry and RFNL over many months can eventually identify actual disease progression, confirmation of which is accompanied by permanent loss of tens of thousands of axons. Evidence confirms that appropriate early intervention can substantially reduce the financial burden of glaucoma.[8]

Perhaps surprisingly to most readers, worldwide epidemiologic evidence[9–15] indicates that a substantial majority of individuals with pathologic primary open angle glaucoma (POAG) have normal eye pressures, most of whom will remain undetected and untreated because of overreliance on tonometry as a diagnostic test.[16,17] Instead of focusing on therapeutic approaches to help mitigate all forms of glaucoma, vast resources continue to be expended on unwarranted prophylactic treatment of nonglaucomatous ocular hypertensives susceptible to adverse effects of topical therapy, but highly unlikely to develop even mild disease in its absence.

The International Society for Clinical Electrophysiology of Vision[18] standard clinical electrophysiology methods employed in this study existed and were applied to the assessment of glaucomatous patients well before the commercial advent of either automated perimetry or RNFL analysis.[19–23] Measurements of visual evoked potential (VEP) were performed in our clinical population using the same contrast reversal stimuli used to generate steady-state retinal depolarization at the ganglion cell layer via pattern electroretinography (PERG). These long-established clinical technologies together provide dynamic functional information that actually helps segregate ocular from visual pathway pathology, and their independent and combined ability to detect glaucomatous functional abnormality has been long established (see below). These methods are applied routinely in our clinic to help identify active disease, implement therapy, and observe for positive effects of treatment. The findings reported here are direct manifestations of this integration of clinical electrophysiology in daily glaucoma patient management. Better understanding of extant dynamic function can assist in more timely and appropriate management of individual glaucoma patients, and may, as in this case, provide important insights into one important age-related neurodegeneration with potential clinical relevance to others.

Until very recently, it was widely assumed that glaucomatous neurodegeneration was entirely modulated via local stressors (ocular hypertension, genetic predisposition, circulatory compromise, or metabolic dysfunction) in genetically paired, phenotypically and environmentally identical, but independently afflicted eyes. It is now apparent that such etiologic variables contribute to meticulous central nervous system (CNS)-coordinated apoptotis throughout the visual pathway,[24] with clinical evidence of potential compensatory neuroplastic remodeling of the ocular dominance columns in the striate cortex.[25]

In glaucoma, the nerve fiber layer loss that corresponds anatomically with the pattern of permanent VF loss is accompanied by the loss of corresponding neurons in the lateral geniculate nucleus (LGN) of the midbrain.[26] Damage to both magnocellular and parvocellular pathways has been shown in experimental models of glaucoma.[27,28] Not only the LGN, but the optic radiations and visual cortex may be similarly affected in glaucoma.[26] It was initially presumed that these corresponding alterations in retinal, optic nerve and brain anatomy were an atrophic consequence of decreased ocular neural input, but it is now evident that the CNS modulates specific functional changes that precede programmed cell death within the eye, as well as triggering the final apoptotic processes therein,[24] with one very practical consequence being to maximize the binocular VF.[25,29,30] It is thus reasonable to consider the possibility that the CNS might similarly orchestrate necessary sacrifices in the paired-eye/brain complex to minimize the practical pathologic consequences of less spatially oriented dynamic visual dysfunction that is also attendant to the glaucomatous disease process.

VEPs are light stimulus–induced electrophysiological signals extracted from the electroencephalographic activity. VEPs depend on functional integrity of central vision at all levels of the visual pathway including the retina, optic nerve, chiasm, optic tracts, optic radiations, and the occipital cortex.[18] VEP has been used extensively for the diagnosis and management of glaucoma.[31–35] Evidence exists to show that

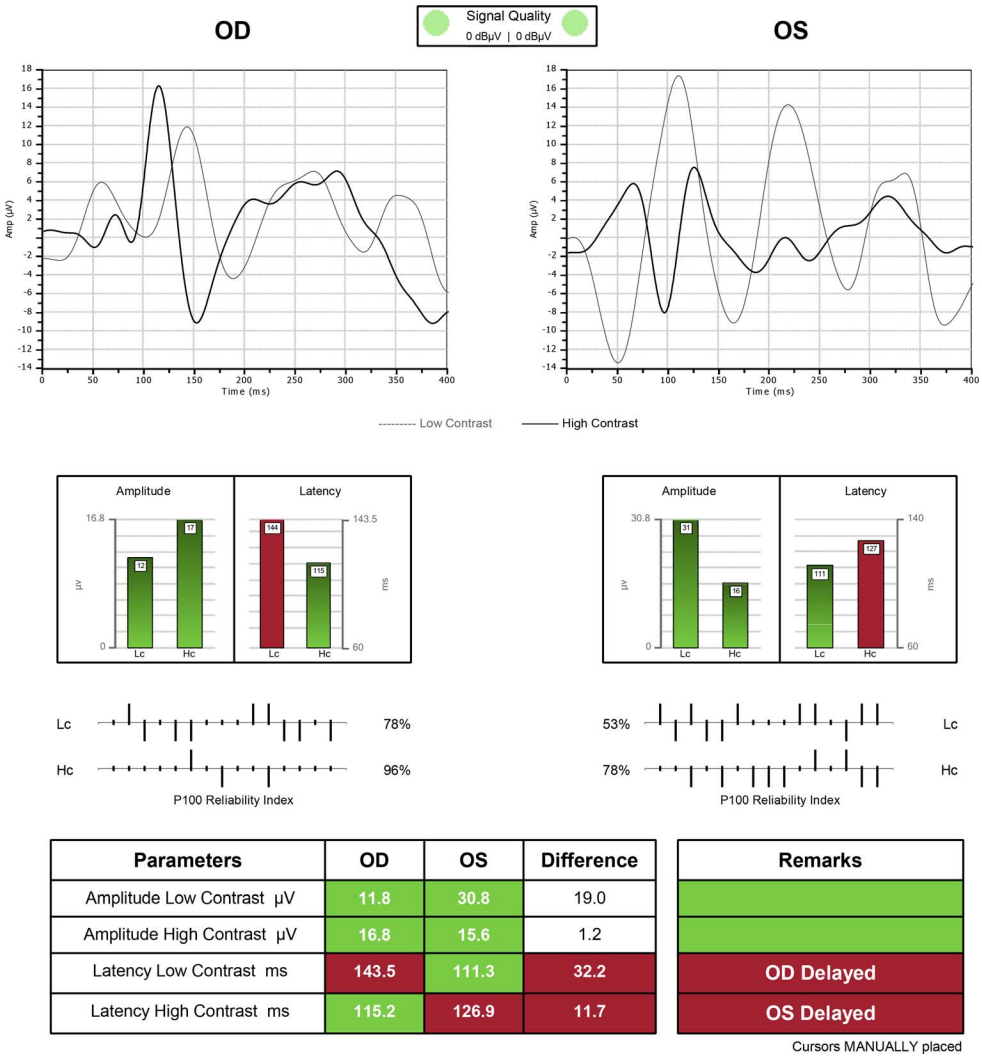

Figure 1. Printout of typical patient of from a patient in the primary study group, with one pathological latency delay in each eye. Consistent with the majority in this cohort, this patient demonstrates complementarity of the Lc and Hc responses in the paired eyes.

pattern reversal VEP stimuli provided at different levels of contrast can help differentiate the dynamic functional status of the magnocellular and parvocellular pathways.[35] The magnocellular pathway comprises relatively few (~150,000) larger ganglion cell axons that conduct lower resolution, higher speed information from larger receptive fields. The parvocellular pathway is comprised of more numerous (~1.2 million) smaller axons that tend to conduct slower speed, higher resolution visual information.

Glaucomatous eyes show higher tendency for delayed VEP latency with the system used in this study than do normal eyes.[31] We reaffirmed this among our own clinical population earlier with the same device used in this study.[32] While evaluating those data we observed that an unexpectedly high proportion of diseased patients showed high-contrast (Hc) latency delay in one eye and low-contrast (Lc) delay in the fellow eye (Fig. 1). To objectively assess whether such a potential binocular compensatory tendency might be truly prevalent among our clinical population, we initially evaluated all subjects undergoing VEP who exhibited only one pathological level of latency delay per eye (the primary study population). If the proportion showing the same deficiency (Hc or Lc) in both eyes proved to be significantly lower than those with Hc latency delay in one eye and Lc latency delay in the other, we would evaluate a larger, more inclusive group of patients who had as few as one and as many as three pathologic levels of Hc or Lc latency between in the paired eyes (the secondary study population) to see if any compensa-

tory phenomenon might also apply in more asymmetrically afflicted paired eyes with milder or more severe dynamic dysfunction.

Methods

This prospective study was conducted at the San Antonio, Texas WESMDPA Glaucoma Service clinic among its active clinical population, in compliance with the Helsinki Declaration. The protocol was proactively approved under a noninvasive masked alphanumeric clinical record waiver by the University of the Incarnate Word institutional review board.

The primary study population included 64 eyes of 32 patients with general clinical, optical coherence tomographic and perimetric evidence of chronic open angle glaucoma (COAG) who met the entry criteria. There were 20 females (62.5%) and 12 males (mean age 55.6 years). The secondary study group included 286 eyes of 143 patients (mean age 59.2 years). All subjects underwent a complete ophthalmologic examination, including visual acuity, slit-lamp biomicroscopy of the anterior segment, gonioscopy, intraocular pressure measurement, manifest refraction for best-corrected visual acuity (BCVA), and ophthalmoscopic examination of the posterior segment. Findings were documented in their Health Insurance Portability and Accountability Act of 1996–compliant electronic medical record (MDLand.com). Nearly all subjects had also undergone both automated perimetry (see details below) and optical coherence tomography (Optovue, Carlsbad, CA) to help verify their glaucoma diagnosis and confirm macular integrity, results of which were fully documented.

Eyes were categorized as POAG if they had open iridocorneal angle, characteristic optic nerve and RNFL appearance (local narrowing, notching, or absence of the neuroretinal rim in the absence of disc pallor elsewhere; focal or diffuse RNFL defect). POAG eyes had corresponding VF defects defined as mean deviation (MD) and pattern standard deviation (PSD) outside 95% normal confidence limits and glaucoma hemifield test outside normal limits in at least one eye and at least early evidence of similar pathology in the fellow eye.

Inclusion criteria for the study was as follows: for the primary study group, each eye exhibits a single (Hc or Lc) VEP latency abnormality (assigned a red histogram bar on analytic printout; Fig. 1 shows one example); for the secondary study group, the two eyes together exhibit as few as one, or as many as three (Hc or Lc) VEP latency abnormalities (assigned red histogram bar[s] on analytic printout).

Exclusion criteria were: (1) BCVA worse than 20/40; (2) spherical refraction greater than or equal to 5.0 diopters (D) and cylinder correction greater than or equal to 3.0 D; (4) history of intraocular surgery (with the exception of uncomplicated cataract surgery); (5) media opacity affecting the ability to obtain good quality VEP/PERG signal.; (6) other diseases affecting the VFs (e.g. demyelinating diseases, or diabetic retinopathy); (7) medications known to affect VF sensitivity (e.g., vigabatrine, lamotrigine); and (8) neuropathies or other disorders that could affect the VEP like epilepsy, stroke or traumatic brain injury.

Electrophysiology

The VEP method used in this study was a modified extension of the Diopsys Enfant NOVA system (Diopsys Enfant Amp 100; Diopsys Inc., Pine Brook, NJ). The stimulus was presented on an Acer V173 17-inch liquid-crystal display monitor running at 75 frames per second (Acer, Inc., Hsinchu City, Taiwan). Output over time was verified using a luminance meter Mavo-Spot 2 USB (Gossen, GmbH, Nurnberg, Germany). Diopsys surface electrodes (10 mm) with commercially available skin preparation and EEG paste (Nuprep® Skin Prep Gel and Ten20® Conductive Paste, DO Weaver and Company, Aurora, CO) were used for recording the VEP. NOVA-ERG lid sensors were used for PERG studies performed at the same visit for a subset of patients. Synchronized single-channel VEPs were recorded, generating time series of 512 data points per analysis window. The room luminance was maintained at scotopic conditions (<0.3 cd/m^2). Preadaptation was not required for the VEP recordings. Each phase reversal was set at 500 ms and was monitored for effects due to blinking or eye movement. A technique for artifact rejection was used during VEP data recording; if half or more of the phase reversals were rejected, then the entire run was rejected. The maximum run time for a single test was limited to 20 seconds (40 single VEPs at a frequency of 1 Hz). Each complete VEP protocol was comprised of multiple test instances. One complete VEP protocol presented the stimulus for a maximum of 1 minute and 46 seconds. The square black/white checkerboard pattern reversal stimulus had a height and width of 27 cm with checks size of 29.0 minutes of arc. A red cross was used as a fixation target. The diameter of this target was

approximately 1 cm with a ring thickness of 1.5 mm. The target cross was centered on the stimulus. Two types of contrast patterns were used in the study. The two patterns used represented Lc (Michelson contrast of 15%, white checks with 122.9 cd/m^2 and black checks with 101.1 cd/m^2) and Hc (Michelson contrast of 85%, white checks with 122.9 cd/m^2 and black checks with 9.6 cd/m^2). During each recording session, the contrast polarity of each stimulus check was temporally modulated at a reversal frequency of 1 Hz (2 pattern reversals equates to 1 reversal cycle); therefore, each reversal occurred at 2 Hz or twice per second. This stimulus is termed a pattern reversal stimulus and has a duty cycle of 50%. The 15% and 85% contrast stimuli were presented for each eye for 20 seconds while the untested eye remained covered. The right eye was standardly chosen as the first one to be tested for all patients. In preparation for VEP recording, the skin at each electrode site was scrubbed with Nuprep (D.O. Weaver & Co., Aurora, CO) using a cotton gauze pad. Electrodes were fixed in position with a small gauze pad applied with Ten20 conductive paste (D.O. Weaver & Co.). Electrode impedance was maintained below 10 kΩ and typically kept below 5 kΩ. The gain of the EEG analog amplifier/filter module in the Enfant system was set at 10,000 with band-pass filter frequency range of 0.5 to 100 Hz. The EEG signal was sampled at 1024 Hz using the Enfant system's analog-to-digital (A/D) converter. The EEG filter gain of 10,000 is the only gain in the entire data acquisition path, including the (A/D) 12-bit convertor. The A/D convertor offers a series of bipolar voltage ranges. For this study, the A/D converter was programmed to operate across a voltage range of (–)1.25 V to (+)1.25 V with a resolution of 610 mV/quantum.

Patients undergoing concomitant PERG assessment underwent steady state (15 reversals per second; 7.5 Hz) with Hc and Lc, respectively, stimulation. All patient testing was carried out after proper refraction with correction in place for a 24″ testing distance, with the right eye tested first. Hc stimuli were presented for 25 seconds, followed by Lc stimuli, also for 25 seconds. Magnitude D (MagD) is an integrated waveform analysis measure that takes account of both PERG magnitude (Mag) and phase variability throughout the recording. When steady state PERG recordings remain in phase throughout the testing period MagD will approximate to Mag. When waveforms tend to fall out of phase throughout testing the MagD values drop accordingly. For all qualifying subjects with concomitant PERG studies available for analysis linear regression analysis was performed to evaluate the relationship for each eye between Lc and Hc PERG Mag and Lc and Hc PERG MagD. In addition, the relationship between Hc and Lc PERG Mag and MagD between the right and left eyes was similarly evaluated.

In all cases, for both VEP and PERG, the stimulus was viewed through nondilated pupils with optimal refractive correction in place. The viewing distance was set to 39 inches for VEP and 24 inches for PERG, yielding a total display-viewing angle of 15.5° and 24°, respectively.

Output parameters from the VEP system include amplitude and latency measures for each of the contrast stimulus protocols. The amplitude parameter (measured in microvolts) reflected the strength of the signal being transmitted through the visual pathway, essentially an indication of neural structural integrity, including axons. The latency parameter (measured in milliseconds) was a measure of the length of time for signal transmission along the primary visual pathway. The combination of these two parameters is helpful in assessing the overall health of the visual pathway. It is implicit that the latter measure could only apply to extant axons with normal or subnormal functionality, whereas the former measure would be reflective of the composite of lost and potentially recoverable but dysfunctional axons.

Subjects underwent three consecutive VEPs and PERGs examinations using the Diopsys NOVA fixed protocol. All examination procedures were carried out in accordance with manufacturer's recommendations. To assess intersession repeatability, nine subjects returned on another day for repeat examination. The confidence interval $m - E \leq m \leq m + E$ was computed iteratively to estimate the corresponding Z value using $E = Z/(2\sqrt{n})$, where n is the number of patients. Hc were plotted against Lc latency values for all 64 eyes to determine whether a significant inverse correlation existed for these values among the 32 subjects.

The coefficient of repeatability (CR) is the value below which the absolute differences between two measurements would lie within 0.95 probability. It is calculated by multiplying the within-subject SD by 2.77. The CR is quantified in the same units as the assessment tool. The relative repeatability (RR) is the ratio of the CR to the mean value of the measurements. A lower RR represents greater repeatability, and less than 50% is considered acceptable when measuring biological metrics. [r4] The coefficient of variation (CV) is a standardized measure of disper-

sion. It is defined as the ratio of the SD to the mean, and is expressed as a percentage.

Visual Field

Standard automatic perimetry (SAP) tests were obtained from all eyes using Humphrey Field Analyzer II, Swedish Interactive Thresholding Algorithm (SITA) Standard strategy[37] program 24–2, and/or with the Humphrey Frequency Doubling Technology Matrix using the full threshold 25° testing algorithm (both devices: Carl Zeiss Meditec, Inc., Dublin, CA). All included tests were of good reliability (false-positives, fixation losses, and false-negatives $\leq$25% with no observable testing artifacts). VFs were repeated at least two times to confirm the reproducibility of the VF defects. All those meeting pre-established reliability criteria were assessed.[25,29] Right and left VF pairs were evaluated without reference to the NFL or ERG findings to determine, for each eye, whether loss was predominantly central (C), peripheral (P), or indeterminate (N). Masked binary analysis of Hc and Lc VEP latencies versus C and P was then performed for subjects in the primary study group.

Results

Diopsys NOVA-LX system was used to measure VEP Hc and Lc latency in 440 adult glaucoma suspects and established patients. A majority produced either bilaterally normal VEP latency results or total Hc and Lc VEP latency abnormality in both eyes. Thirty-two patients (64 eyes) produced one pathological Hc or Lc latency delay in each eye (the primary inclusion criterion for this translational study). One hundred forty-three patients (286 eyes) had one, two, or three forms (Hc or Lc) of pathologic VEP latency delay in their paired eyes (the secondary inclusion criterion for this translational study).

Among the 64 eyes exhibiting a single (Hc or Lc) VEP latency abnormality in each, 32 had mild, 15 moderate, and 17 severe glaucoma using standard perimetric scoring criteria[15] obtained within 2 to 4 months of their electrophysiologic assessment (mean age was 53 ± SD 9 years; range, 40–84 years; 69% female). For all 64 of these eyes VEP amplitude values were normal. All VEP latency measurements had reliability greater than or equal to 70%. There was no overall preference for VEP latency at either contrast level between right and left eyes. There were 24 of 32 patients who had delayed Lc latency in one eye and delayed Hc latency in the other; only eight had delayed latencies for the same contrast category in both eyes. This corresponds to approximately 99.5% confidence ($P = 0.005$) that this difference could not be a consequence of chance predicted by the H_0 ($r = 0.5$). In addition, a remarkably strong inverse correlation ($P = 0.0000003$) was observed between the Hc and Lc latency values plotted for the 64 paired right and left eyes (Fig. 2).

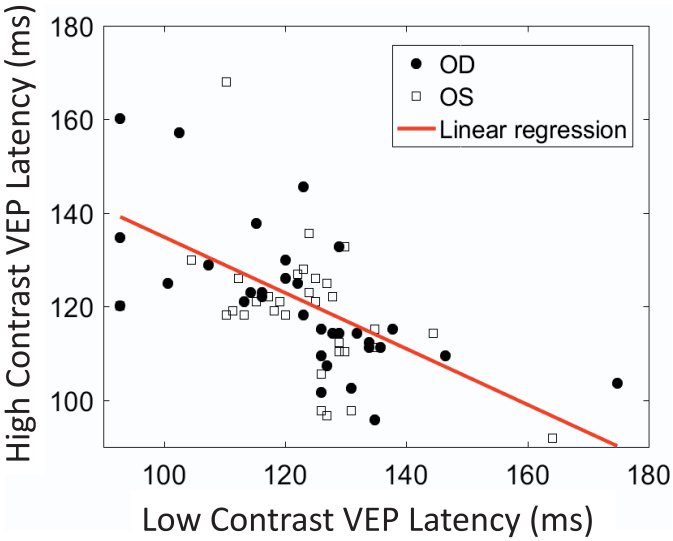

Figure 2. A highly significant inverse association ($P = 0.0000003$) was observed between the Hc and Lc latency values plotted for the 64 right and left eyes in the primary study group (see Results for details).

Of the 32 primary study group patients, 14 (44%; 10 female, 4 male) had qualifying PERG data available for analysis. Their mean age (54.6 years) did not differ significantly from the 18 patients without PERG data ($P = 0.88$). There was no statistically significant difference between Mag or MagD between their right and left eyes under either Hc or Lc stimulus conditions. Linear regression analysis revealed significant positive correlations between Hc and Lc Mag ($P = 0.01$, $r^2 = 0.22$) and between Hc and Lc MagD ($P = 0.0002$, $r^2 = 0.41$; Fig. 3, panels A and C). In addition, there was significant positive correlation between right and left eyes for Mag ($P < 0.0001$, $r^2 = 0.63$) and MagD ($P = 0.0001$, $r^2 = 0.44$; Fig. 3, panels B and D).

In the masked paired VF assessment, 60 eyes from 30 patients (94%) in the primary study group were evaluated. Forty-eight eyes (80%) of 24 patients (mean age 55.6 ± [standard error of the mean] 3.1) qualified with VF outcomes that met inclusion criteria. Six pairs had VF graded N, 66.7% of eyes

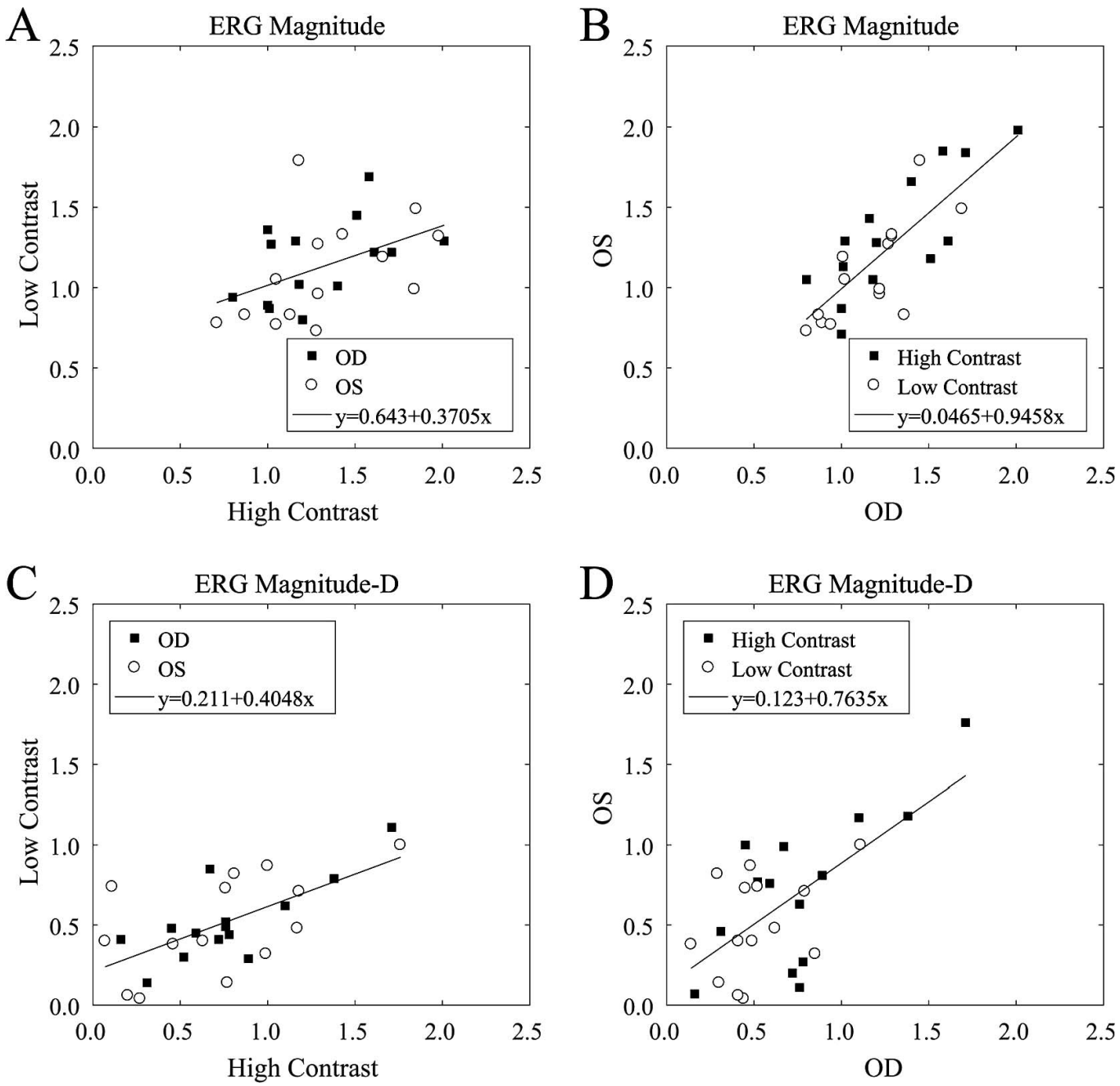

Figure 3. Linear regression analysis among the primary study group revealed significant positive association between pattern electroretinographic Hc and Lc Mag ($P = 0.01$, $r^2 = 0.22$; *Panel A*) and between Hc and Lc MagD ($P = 0.0002$, $r^2 = 0.41$; *Panel C*). Highly significant positive associations were also found between right and left paired eyes for Mag ($P < 0.0001$, $r^2 = 0.63$; *Panel B*), and MagD ($P = 0.0001$, $r^2 = 0.44$; *Panel D*).

with dominantly C VF loss showed Lc abnormality, and 62.5% of eyes with dominantly *P* loss showed Hc abnormality ($P = 0.0441$; mean 0.2917; confidence interval 0.0081–0.5753). This equates to a borderline significant Hc association with midperipheral loss versus Lc association with pericentral loss ($P = 0.04$).

The secondary population ($n = 286$ eyes), which included the above symmetrically abnormal subjects together with individuals exhibiting both mild and severe subtotal asymmetric VEP pathology, was assessed by repeating the plotting of Hc versus Lc latency. A comparable outcome was observed with this much more inclusive glaucomatous population, with a highly significant negative correlation again

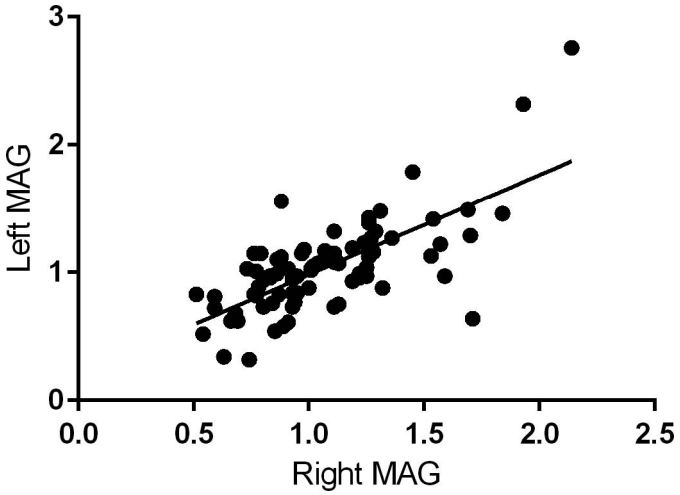

Figure 4. Positive association of low contrast PERG magnitude values from right and left eyes of the secondary study group, demonstrating that dynamic ganglion cell function tends to be symmetrically compromised even in paired eyes that have asymmetric degrees of PERG dysfunction. Essentially equivalent associations were observed for high contrast PERG magnitude values (see Results for details).

arising between Lc (x: range, 92–170 ms) and Hc (y: range, 87–159 ms) latency values (Fig. 4; $y = -0.20x + 141.8$; $R = 0.20$, $P = 0.0005$). Of these patients, 81 (162 eyes) had undergone PERG evaluation with Hc and Lc stimuli at the same clinical appointment during which they underwent their VEP assessment. Among this larger cohort, PERG Mag values again showed a very strong positive association between the paired eyes (PERG Lc Mag OD(x) vs. OS(y); Fig. 5; $y = 0.78x + 0.20$, $R^2 = 0.49$, $P < 0.0001$; PERG Hc Mag OD(x) vs. OS(y), $y = 0.78x + 0.20$, $R^2 = 0.40$, $P < 0.0001$).

Discussion

VEP has been used previously for the evaluation of magnocellular and parvocellular systems. For this purpose different authors have used various levels of low-end contrast stimulation, one as low as 1.3%,[38] another 10%,[39] and one as high as 24% Michelson contrast.[40] Our present findings, differentiating pathways using 15% Michelson contrast for low and 85% for high, expand upon our earlier observations published in this journal confirming CNS conservation of complementary bilateral visual function in glaucoma based on VF refined data analysis.[25,29,30] It now appears that when both magnocellular and parvocellular function cannot be fully supported by either eye, one eye will tend to favor high-speed low-

Parameters	OD	OS	Difference	Remarks
Amplitude Low Contrast µV	6.4	5.5	0.9	
Amplitude High Contrast µV	8.4	7.5	0.9	
Latency Low Contrast ms	131.8	124.0	7.8	OD Delayed
Latency High Contrast ms	114.3	135.7	21.5	OS Delayed

	OU
Latency Low Contrast ms	124.0
Latency High Contrast ms	114.3

⇨ Complimentary Effect?

Figure 5. Presumed likely compensatory binocular consequence of the strong bilateral inverse bias for high- versus low-contrast latencies observed among glaucomatous eyes in both the primary and secondary study groups.

resolution function and the fellow eye will tend to favor lower speed, higher resolution function (Fig. 5). If so, this natural adaptive compensatory process, to cope with loss of dynamic neural processing capacity during glaucomatous disease progression, might be anecdotally compared with iatrogenic optical monovision correction (one eye myopic, the other emmetropic) to compensate for presbyopia. This apparent adaptive bilateral VEP (visual pathway) neuroconductive bias arises despite nearly symmetric bilateral function for both Hc and Lc at the PERG (ganglion cell) level. Such complementarity could not exist in functionally independent eyes. While the VF findings suggest that the spatial jigsaw effect is weakly associated with this dynamic function complementarity, the significance level of the observed correspondence of spatial with dynamic functionality seems too feeble for spatial factors to account for the profound bilateral VEP latency biases observed here. The Hc/Lc compensatory effect would seem more likely to be among the primary adaptations that arise first, and which may subsequently influence patterns of VF loss.

The fact that monocular and binocular responses in the human visual cortex to similar visual stimuli produce very different topographical responses in electrical brain activity[41] highlights the likely future importance of simultaneous binocular testing. Others have identified CNS-directed compensatory mechanisms at work in patients with analogous age-related disorders, including Alzheimer, Parkinson, and Huntington Diseases.[41–44] Bilateral CNS modulation of other well-established chronic ocular disorders is also now an open therapeutic field. Rabin et al.[45] recently described a new method for diagnosis of normal and abnormal color vision with cone-specific VEPs. They subsequently used this methodology to demonstrate that despite identical genetically heritable deficiencies

in both retinae, binocular compensation for red-green hereditary color vision deficiency (CVD) brings the afflicted individual close to normal when both eyes are open. Binocular VEP signals from CVD anomalous trichromats were nearly three times larger than their monocular VEPs for the cone type corresponding to their CVD.[46]

The results we report here in both symmetrically and asymmetrically compromised glaucoma patients suggest a powerful force is at work to produce the bilateral VEP Hc and Lc latency biases seen. Among the possible CNS candidates explaining this are an established gain-control mechanism that produces much larger VEPs for transient onset stimuli.[47,48] Onset stimuli were not used here, but the relatively slow reversal rate applied for these patients might bring it into play. Gain control effects can increase VEP amplitude by 10 to 15 times relative to those obtained for rapid contrast reversal. Corticothalmic feedback has been suggested as a driver of this.[49] This effect is weaker at Lc.[46] Cortical atrophy is already established as a coexisting pathology in glaucoma,[26] as well as defective myelination within the optic radiations.[50] Thus, in a minority of subjects asymmetric disruption of the gain-control might occur and have knock on effects for latency, which is generally more reliable than amplitude in evoked potential recordings. This might have a homonymous expression, and other mechanisms are bound to come into play in this newly appreciated CNS-controlled dynamic bilateral compensatory mechanism. The VEP Hc and Lc latency asymmetry reported here has not been observed among healthy individuals in the same community (Trevino R, et al. *IOVS*. 2016;57:ARVO E-Abstract 3605), so this newly recognized adaptive mechanism should provide classification power for distinguishing healthy eyes from glaucomatous eyes, poorly compensated from well-compensated glaucoma, and glaucoma from other ophthalmic conditions.

There is clearly much exciting work to carry out to fully characterize the nature of this further display of coordinated compromise in a well-established ocular age-related neurodegenerative disorder. Electrophysiological data that can readily identify previously unrecognized features of the disease can now be collected and analyzed directly in the eye clinic, a clear manifestation of the translational clinical relevance and practical utility of this long-established technology. The clinical renaissance of classic electrophysiology in the management of open angle glaucoma, facilitated by advanced microprocessor capability and reliable disposable adhesive skin electrodes, will lead to more rapid determination of individuals actually at risk of progression,[51] and should continue to contribute significantly to our better understanding of the role of the brain in the modulation of glaucoma and other age-related neurodegenerative disorders.

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